

Johnson & Johnson

410 GEORGE STREET
NEW BRUNSWICK, NJ 08901-2021

July 7, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0571; Draft Guidance for Industry on Drug Substance Chemistry, Manufacturing and Control Information; 69 Federal Register 929 (Jan 7, 2004)

Dear Sir/Madam:

The attached comments on the above draft guidance are submitted on behalf of Johnson & Johnson. We actively participated in and fully agree with the comments submitted by PhRMA. In addition we feel that this document is so significant that it is important to comment both collectively and as individual companies.

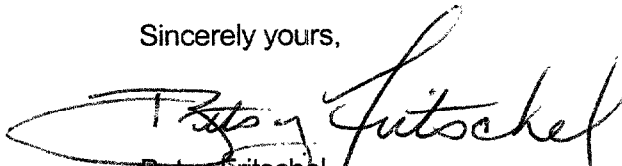
We appreciate the new concepts of PQIT, interim acceptance criteria and sunset testing that the Agency has incorporated into this document. Additionally, the clarification that applicants need not investigate different physical forms of the drug substance if the conditions which produce those forms deviate significantly from the filed manufacturing process is helpful.

We are however concerned about the numerous instances where additional detail is requested. We realize that this document has been many years in drafting and it may predate the Agency's current science and risk based approach. In our comments you will find specific instances where we have attempted to bring the focus to the critical items and to suggest deletion of unnecessary information. This unnecessary information adds complexity and time both to the preparation of the filing as well as the review. We would like to suggest a more concise and science- based approach, which we feel would be mutually beneficial.

Regarding Attachment 1 and 2, PhRMA has suggested that the entire approach be reconsidered. We completely support this approach and would welcome the opportunity to discuss this with the Agency either via PhRMA or any other venue that is mutually convenient. Although our preference is a total reconsideration of this section, we have included specific line item comments.

Our detailed comments are provided in an Excel spreadsheet in the attachment. This spreadsheet includes the line number, section number, proposed edit, and rationale for each comment. You will note in the final column we have included the same rating of "importance" used by PhRMA. Due to the large number of comments, we did not include any "minor" comments. Please feel free to contact me if you need further assistance or have any questions regarding these comments.

Sincerely yours,


Betsy Fritschel
Director, Quality and Compliance Services

2003D-0571

CZ6

**Johnson & Johnson Comments on:
Draft FDA Guidance “Drug Substance – CMC Information”
(Docket No. 2003D-0571)
January 2004**

Line Number	Draft Guidance Section	CTD Section Number	Comments and Proposed Edits. (The bold text indicates suggested additions and the strike through indicates proposed deletions)	Rationale or Comment	Importance 1= Major 2= Moderate 3=Minor
222 -285	II.D.2		Delete lines 222-285 entirely	If a DMF is used to submit Drug Substance information, this section recommends that information be repeated in the NDA. We do not agree with this approach. It is important not to duplicate information in the DMF and the application, requiring updating of both a DMF and an application when post-approval changes are made and increasing compliance risks. Additionally this is inconsistent with 314.420 which allows for use of DMFs to submit information. Also, in some cases the proprietary information may not be available to the applicant.	1
381	IV.A	S.2.1	The addresses should be for the location where the relevant manufacturing or testing operation will be performed. Addresses for corporate headquarters or offices need not be provided. Building numbers or other specific identifying information should be provided for multifacility campuses.	Since a facility is a single GMP inspected site then it is irrelevant which individual building is used. Post Approval Changes of buildings is not even reportable under BACPAC I and Changes to NDA Guidances. This is an additional request for detail with no added scientific value.	1
390	IV.A	S.2.1	To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application, this information may be listed in this section or elsewhere in the application such as the FDA356H form or the administrative information section. Facilities should be ready for inspection when the application is submitted to FDA. Facilities should be ready for inspection within timeframes specified in current guidances.	Consistency with other FDA regulations and guidances.	2

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398	IV.B	S.2.2	A flow diagram and a complete description of the processes and process controls that will be used to manufacture the drug substance or derive it from a biological source should be provided in S.2.2.	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality.	1
406	IV B.1	S.2.2	Flow Diagram	Flow Diagram (S.2.2.1)- The amount of information requested for inclusion on the flow diagram is too extensive and is better captured in the Narrative Description of the Manufacturing Process and Process Control (S.2.2.2). We suggest removing lines 411-436 and including a clearer description of whether they want a structural flow diagram or a block flow diagram.	1
440	IV.B.2	S.2.2	A narrative description of the manufacturing process that represents the sequence of manufacturing steps undertaken and the scale of production should be provided.	This is an additional request for detail with no added scientific value.	1
442	IV.B.2	S.2.2	The description should identify significant all-process controls and the associated numeric ranges, limits, or acceptance criteria.	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality. This is an additional request for detail with no added scientific value.	1
450	IV.B.2	S.2.2	Starting materials or intermediate used in each step, with chemical or biological names and quantities or molar ratios specified	Absolute quantities do not necessarily add value. Molar ratios are often more meaningful.	1
452	IV.B.2	S.2.2	Solvents, reagents, and auxiliary materials used in each step, with chemical or biological names and quantities or molar ratios specified if critical	Absolute quantities do not necessarily add value. Molar ratios are often more meaningful. For solvents, reagents and auxiliary materials the amount is often not critical. This is an additional request for detail with no added scientific value.	1
454	IV.B.2	S.2.2	Type of equipment (e.g., glass lined reactor when stainless steel could affect reaction Centrifuge) used, including materials of construction when critical	Delete comma so that type of equipment is only specified when critical	2

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457	IV.B.2	S.2.2	All Significant process controls and their associated numeric ranges, limits, or acceptance criteria, with critical process controls highlighted	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality. This is an additional request for detail with no added scientific value.	1
466	IV.B.2	S.2.2	Identification of manufacturing steps that use recovered recycled solvents or auxiliary materials	Define recovery and recycle.	1
471	IV.B.2	S.2.2	Identification of processes that involve combining intermediate or drug substance batches, drug substance and a diluent, or two or more drug substances	Combining intermediates for charging into the next process step is common practice in API manufacturing. Blending of smaller batches or portions of batches meeting specification to achieve a larger batch size is also common practice in API manufacturing. The traceability of the blended batches is a cGMP issue not a filing issue. No added value to file this kind of information	1
473	IV.B.2	S.2.2	Typical Yield ranges (weight and or percent) for each manufacturing step	Yield ranges should be typical not implying exact amount. If molar ratios are used then percent is more appropriate than weight .	1
479	IV.B.2	S.2.2	Storage and transportation conditions for biological starting materials	Clarification required between cell culture and natural products.	1
483	IV.B.2	S.2.2	Procedures used to maintain traceability of all intermediate and drug substance batches back to the batches of the starting material	Delete. This is a GMP issue not a filing issue.	1
500- 517	IV.B.2	S.2.2	Delete lines 500 to 517 entirely.	This text should be in the definition. This section should be clear as to which process controls are to be filed.	1
521	IV.B.2	S.2.2	All Significant process controls, critical or otherwise, should be included in the description of the manufacturing process.	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality. This is an additional request for detail with no added scientific value.	1
538	IV.B.2	S.2.2	Delete lines 538 to 541 entirely. All critical process controls should be identified in the Description of Manufacturing Process Section with details provided in Section S.2.4.	This is an additional request for detail with no added scientific value.	1

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561	IV.B.2	S.2.2	However, validation data, when warranted to support the operation, should be provided in S.2.5. (see section IV.E for possible situations when process validation information is warranted.). Add note that validation information is normally reviewed during facility audits and is not included in the filing.	See line 877.	1
576	IV.B.2	S.2.2	Repetition of multiple reaction steps is should be considered very carefully to be reworking, rather than reprocessing (see section IV.B.3.b) because the material to be re-introduced into the process may not be similar to the original reactant. Repetition of multiple reaction steps is discouraged.	Repetition of multiple steps is discouraged but should not be defined as reworking.	1
580	IV.B.2	S.2.2	Reprocessing a drug substance, after it has been released by the quality control department, to bring the material back into conformance with its specification may be allowable in certain instances. Examples include reprocessing a hygroscopic material to lower water content, milling to meet a different particle size specification, or repurification of aged material to conform to approved specification.	Insert deleted text from line 658 which is more consistent with the definition of reprocessing than reworking.	1
605	IV.B.2	S.2.2	Repetition of multiple reaction steps is considered to be reworking because the material to be reintroduced into the process is not similar to the original reactant. Repetition of multiple reaction steps is discouraged because of concerns relating to unexpected impurities and degradants.	Repetition of multiple steps is discouraged but should not be defined as reworking.	1
647	IV.B.2	S.2.2	The regeneration of materials such as column resins and catalysts should be described in S.2.2 if these operations are performed. The process controls for regeneration operations should be provided. Controls on regenerated material can include, for example, a maximum number of times the material will be regenerated and/or tests to determine the continued suitability (e.g., column efficiency) of the material. When appropriate, specifications for regenerated materials should be included in S.2.3.	This a cGMP issue vs. filing issue. Full information on regeneration will not be available at the time of the filing.	1

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658	IV.B.2	S.2.2	or (2) a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its specification (e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria).	This is inconsistent with the definition of rework. This is reprocessing.	1
669	IV.C	S.2.3	Information on the materials (starting materials, reagents, solvents, auxiliary materials, and diluents) ...	Add definition for reagent, solvent and diluent to the Glossary.	2
674	IV.C	S.2.3	Add principle of PQIT and sunset tests for Section S.2.3 Starting Materials and Raw Materials	This concept seems very appropriate as the new guidance is asking for additional tests and specs for Starting Materials and Raw Materials	1
684	IV.C.1	S.2.3	The starting material for application purposes can differ from the active pharmaceutical ingredient (API) starting material, which marks the point in the manufacturing process from which appropriate GMP should be applied (as defined in ICH Q7A: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients).	ICH Q7A intended for the application to define the starting material for synthetic processes.	1
688	IV.C.1	S.2.3	In general, the starting material for filing purposes and API starting material as defined by ICH Q7A should be the same for a synthetic drug substance.	No need for difference with ICH Q7A.	1
689	IV.C.1	S.2.3	However for a drug substance derived from a biological source, the starting material (e.g., plant) and API starting material (e.g., extract) can be different. In this case, information on the biological source (e.g., potential pathogens, herbicides, pesticides) may be is warranted in the application so FDA can evaluate the suitability of the biological source as a starting material for drug manufacture (see Attachment 2)	Based on the number and type of synthetic steps from the biological sources to the API, the company should decide what information on the biological source to file.	1
694	IV.C.1	S.2.3	The recommendations for starting materials provided in this guidance are for application purposes. See ICH Q7A for recommendations on API starting materials.	Not needed based on suggested rewording.	2
713	IV.C.1	S.2.3	A flow diagram	If this is the flow diagram of the full synthesis it is already provided in Section S.2.2. Do not feel that it is appropriate to provide flow diagram for synthesis describing how the starting material was made. Either way this bullet item should be deleted.	1

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741	IV.C.2	S.2.3	At a minimum, Normally the reference should identify the type of analytical procedure used (e.g. GC, HPLC).	"At a minimum" implies that more information is typically filed. For reagents, solvent and auxiliary materials the type of test should provide enough information for the intended use.	1
744	IV.C.2	S.2.3	The tests and acceptance criteria in each specification should be appropriate for the kind of material and its intended use., and should be consistent with the quality of the material used to manufacture the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E).	It should be recognized that at the time of submission of an application only limited number of different lots (and qualities) of solvents, reagents and auxiliary materials may have been used to produce limited number of batches of drug substance. Consistency of specifications with quality of material used is of minor or no importance related to quality of the drug substance. Acceptance criteria have to be related to intended use.	1
769	IV.D	S.2.4	In this section of the application, all only critical process controls should be listed. This could include: operating parameters, environmental controls, process tests and/or all tests performed on intermediates, postsynthesis materials, and unfinished drug substance for the purpose of determining suitability for downstream processing. should be listed and Their associated numeric ranges, limits, or acceptance criteria should be identified.	S.2.4 should describe what is controlling the critical pieces of the process. In some cases this may be parameters and in some cases this may be a test. S.2.4 should be the additional information provided on these critical controls. <i>Strike environmental controls from this sentence and the glossary.</i>	1
772	IV.D	S.2.4	Any of the tests and associated numeric ranges, limits, or acceptance criteria for intermediates, postsynthesis materials, or unfinished drug substance that are judged to be non-critical can be indicated as such. FDA recommends that the noncritical be listed separately from the critical tests to distinguish them from the critical tests that constitute the specification for the intermediate, postsynthesis material, or unfinished drug substance.	Information on non-critical items should not be included in S.2.4.	1

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779	IV.D	S.2.4	For all these critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section (S.2.4) as well. For critical operating parameters and environmental conditions, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section IV.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should be provided as part of the justification. Additional information should be provided in this section (S.2.4) under the following circumstances.	This is information that should be documented in a development report not the filing.	1
789	IV.D	S.2.4	Add principle of PQIT and sunset tests for Section S.2.4 Control of Critical Steps and Intermediates	This concept seems very appropriate as the new guidance is asking for additional tests and specs	1
797	IV.D	S.2.4	In some cases, results from tests performed during the manufacturing process (e.g., material tests or in-process controls process tests, tests on intermediates, postsynthesis materials, or unfinished drug substance) can be used in lieu of testing the drug substance to satisfy a test listed in the drug substance specification.	Post synthesis materials and unfinished drug substance adds additional terminology which creates confusion with no added scientific value. Recommend deleting this terms and editing the glossary to include simplified definitions	1
816	IV.D	S.2.4	When warranted, a specification should be established provided for an isolated intermediate to ensure that it has appropriate quality attributes (e.g., LOD or assay or color or purity, ...) for further downstream processing. A specification for an intermediate should usually include testing for assay and impurities.	Added examples for clarity and deleted last sentence. Very often the assay is a a very gross and ineffective tool for determing the quality of intermediates. The controls normally focus on specific and total impurities which is usually a more effective way of controlling quality.	1
819	IV.D	S.2.4	The specification should be provided in S.2.4.	Redundant	1
839 - 866	IV.D	S.2.4	Delete subsections on Postsynthesis Materials and Unfinished Drug Substance	Post synthesis materials and unfinished drug substance adds additional terminology which creates confusion with no added scientific value. Recommend deleting these sections and editing the glossary to include <u>simplified definitions</u>	1
877	IV.E	S.2.5	Footnote 15: All manufacturing processes should be validated as defined in ICH Q7A.	Clarifying validation requirements and adding ICH Q7A reference.	1

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884	IV.E	S.2.5	However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed (as described above) or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances)	To link to previous paragraph described above	2
892	IV.F	S.2.6	A description to the manufacturing process for the drug substance throughout the various development phases should be provided in S.2.6. The primary focus of this section is the description of the relationship between changes in the manufacturing process or manufacturing site and any associated changes in the chemical or physical properties of the drug substance.	Clarify that this section is not requesting a process development report	1
905	IV.F	S.2.6	The primary stability batches should be manufactured using the same manufacturing processes (e.g., synthetic route) and procedures and a method of manufacture that simulate the process intended for production batches as described in S.2.2. Section 2.6 of the application should contain a description of any significant process differences between the process used to produce the primary stability batches and the process described in S.2.2 (see section IV.B). The description should include an explanation for the differences.	Changes in the manufacturing process between the primary stability batches and the commercial process should be allowed provided they are explained and rationalized. There is an apparent contradiction between the first and second sentences. Proposed edits to eliminated this contradiction.	1
911	IV.F	S.2.6	ICH: Q7A	Add guidance reference to table	2
981	V.A.2	S.3.1	Applicants do not need to investigate the occurrence of different forms under conditions that deviate significantly from the conditions used in the manufacturing processes for the drug substance and drug product.	Very nice clarification	
986	V.A.2	S.3.1	At an appropriate stage of development, the potential for interconversion of solid state forms should usually be investigated in developmental stability studies.	Once it has been shown not to interconvert, the studies should be complete. We should not expect this to be done in on-going API stability monitoring program.	1

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1021	V.B	S.3.2	Impurities that were once present in the clinical drug substance but that have been eliminated by process modifications	The discussion should be limited to those that are relevant to the discussion of safety. Early process impurities are not typically discussed/described under S.3.2. It seems more appropriate that these be discussed in S.2.6 Process Development and that S.3.2 focus on the final process for commercialization.	1
1059	V.B	S.3.2	Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared	No value added to the product.	1
1086	VI.A	S.4.1	When warranted, a specification should be provided for unfinished drug substance If the drug substance is further processed (e.g., micronized) before it is used to manufacture the drug product, the specification for the unfinished drug substance, if there is one, This specification should be included in section in S.2.4.	This is creating a new expectation for a specification for the unfinished drug substance. Need to be clear that while this may sometimes be appropriate, such a specification is not <u>always</u> expected.	1
1090	VI.A	S.4.1	The specification for the mixture should be included in P.3.4 of the application.	This is not stated in the "Draft Guidance for Industry, Drug Product, January 2003"	2
1111	VI.A	S.4.1	The specification from the applicant and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacturer's certificate of analysis (COA).	This is a GMP issue not a filing issue which specific tests are done and which are accepted on CoA because the drug product manufacturer is always responsible for the quality of the drug substance whether or not the test is actually performed. This would also delete footnote 18.	1
1117	VI.A	S.4.1	Tests that can be performed in-process (e.g., Process controls or material tests, intermediate tests, postsynthesis material tests, unfinished drug substance tests) in lieu of testing the drug substance (the results of such tests should be included in the batch analysis report (e.g., Certificate of analysis))	Alignment with suggested changes in the glossary	2
1123	Footnote 19		Certain General Chapters in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the European Pharmacopoeia (EP) and the Japanese Pharmacopoeia (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive.	If pharmacopoeias are harmonized they should not be filed as alternative methods. Either should be acceptable as the regulatory method.	2

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1126	VI.A	S.4.1	Release and shelf life acceptance criteria when both are used	This causes concern and could raise substantial problems. Typically a tighter in-house spec is used for release but only one regulatory spec is filed.	1
1194	VI.B	S.4.2	The analytical procedures used for testing a drug substance should be provided. Recommendations on the content and format of analytical procedures submitted in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation. can be found in ICH Q2A	There is an ICH guidance on this subject. Recommend not referencing an FDA guidance that is not yet issued.	2
1225	VI.C	S.4.3	Analytical validation information, including summary experimental data (e.g., and/or a representative chromatogram(s) with peak identification), for the analytical procedures used for testing the drug substance should be provided.	The full analytical validation package can more appropriately be reviewed on-site during an inspection	2
1231	VI.C	S.4.3	Recommendations on the analytical validation information that should be submitted in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation. can be found in ICH Q2A	There is an ICH guidance on this subject. Recommend not referencing an FDA guidance that is not yet issued.	2
1241	VI.D	S.4.4	Batch analysis data reports (e.g., certificates of analysis (COAs)) should be provided for all drug substance batches used for ...	There is added value in filing separate COAs. Presentation in a tabular format (collated data) is more appropriate and more review-friendly.	2
1246	VI.D	S.4.4	Batch analysis data may be presented either as individual batch analysis reports or as collated batch analysis tables. The batch analysis reports and collated batch analyses data should include a description of the batches. This information can be presented (1) with the batch data as space permits or (2) in a separate table with only the batch identity being included with the batch data.	Tabular presentation of data may be more useful and submission of both individual reports and tabular data is redundant with little if any added value.	2

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1263	VI.D.1	S.4.4	The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification. When warranted, results from additional relevant tests that are not part of the proposed specification may also be included.	There may be examples where additional results are needed to justify the proposed specification. As currently stated in the draft guidance this could be over inclusive.	1
1267	VI.D.1	S.4.4	A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in S.4.2. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC), a more detailed summary describing the changes may be warranted.	We believe this is redundant as the historical information about the analytical procedures is captured in the stability section (S7). We feel that the requirement of a summary of all changes is unduly burdensome. If the principle of the assay changes (titration vs. HPLC) then this should be included, but minor changes (mobile phase and chromatographic conditions) need not be reported.	1
1308	VI.E	S.4.5	However, exclusion of a test that is normally performed on a type of drug substance, one that is recommended in according to ICH Q6A or another relevant FDA guidance, or one that was reported in the batch analyses (S.4.4) should be justified.	Include reference to ICH Q6A	2
1324	VI.E	S.4.5	In these or similar circumstances, an applicant could propose a sunset test protocol for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria.	Thank you. We like this.	

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1338	VI.E	S.4.5	Results from nonclinical (pharmacology and/or toxicology), clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. The primary basis for the acceptance criteria should be the safety and efficacy data not process capability. The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data and analytical and manufacturing capability and variability. Furthermore, any statistical approaches that are used to establish the acceptance criteria should be described.	Concern that basing specifications on process capability rather than safety information will lead to unnecessarily tight specifications that in turn lead to higher cost of manufacture with no added value to the patient (for example tightening down to process capability on residual solvent when that is much lower than ICH Guidance).	1
1347	VI.E	S.4.5	Occasionally, an applicant may wish to propose interim acceptance criteria for a specific test because there is some uncertainty whether the same type of results will continue to be observed for subsequent drug substance batches.	Thank you. We like this.	
1372	VI.E	S.4.5	Acceptance criteria for residual solvents should generally be based upon manufacturing capability.	This is not an appropriate blanket statement. Basing specifications on process capability rather than safety information will lead to unnecessarily tight specifications that lead to higher cost of manufacture with no added value to the patient.	1
1373	VI.E	S.4.5	An applicant should consider the contribution of residual solvents in its drug product excipients when proposing acceptance criteria for residual solvents in the drug substance.	This is more appropriately placed in the Drug Product Guidance.	1
1397	VII	S.5	When the drug substance reference standard is not from an official source, it should be fully appropriately characterized (see Section S3.1 Elucidation of Structure and Other Characteristics).	Clarify that this sentence is only to the drug substance reference standard. Also change "fully" to "appropriately" because some things such as particle size characterization are not value added for a reference standard.	1
1401	VII	S.5	A list of any available reference standards for impurities and intermediates should be included in S.5.	Including a list of intermediate reference standards implies that FDA intends to verify methods for intermediates. This would be an extremely time consuming effort with little value to the patient.	1

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1409	VIII	S.6	A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component. and its specification.	The description of the container closure system should be sufficient to determine its adequacy for use. The significant information (e.g., Material type, additives etc.) should be captured in the description.	1
1411	VIII	S.6	The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.	A brief description of the secondary packaging components should be enough information regardless of whether the packaging component is functional or not.	1
1429	IX.A	S.7.1	The types of studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include for example (1) a summary of stability batches tested, storage conditions used, attributes tested, shelf life acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the label storage conditions and retest or expiration dating period, as appropriate.	Delete reference to shelf life. Acceptance criteria is enough.	2
1438	IX.B	S.7.2	A postapproval stability protocol and stability commitment should be provided.	We realize that this is in CTD. However, this is a new expectation to provide the stability protocol in the filing. We believe that the stability protocol should be available for review during a GMP inspection. Its inclusion in the filing does not add value. Considering that the FDA Draft 1998 Stability Testing of Drug Substance and Drug Products has never been finalized, the reference here should be to ICH Q1A.	1
1478	IX.C.2	S.7.3	Data, other than those from primary stability studies, that support the analytical procedures, the proposed retest or expiry date or shelf life , and label storage statements can be provided.	Consistency with definitions of retest and expiry date in ICH Q7A.	2

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1497	Footnote 26		In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance entitled Stability Testing of Drug Substances and Drug Products. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products.	Continued reference to a Draft Guidance from 1998 that has not yet been finalized adds to confusion.	2
1670	Att 1 - Starting Material		A reagent that contributes a minor structural element to the drug substance (e.g., hydride ion, ammonia, and lower alkyl amine, etc.) ...	We propose the addition of a definition for 'reagent' to the glossary to enable distinction between starting material and reagent.	1
1695	Att 1 - Starting Material		See section II of this attachment for recommendations on the documentation that should be provided for these starting materials.	Add this line for clarification.	2
1701	Att 1 - Starting Material		If the quality of the chemical made for the nonpharmaceutical market is insufficient to ensure consistent quality of the drug substance and the chemical is further processed to produce material of higher quality, the purification operations should be described as part of the manufacturing process of the drug substance (S.2.2).	A potential Starting Material may be purified in order to be suitable for use as an API Starting Material. The filed specification is the control which ensures that the API Starting material is appropriate for use. Therefore It is not value added to include this purification to the filing, the important thing is the specification.	1
1736	Att 1 - Starting Material		If a proposed starting material is inconsistent with a selection principle and a good rationale is provided , this can be acceptable . If should be not justified or the applicant should consider proposing as a starting material a chemical earlier in the manufacturing process that is consistent with the selection principles. The selection of starting material should be based on an overall assessment of all principles.	Don't want to overemphasize any single selection principle. It should be clear that it is the overall assessment that is important.	1
1742	Att 1 - Starting Material		A chemical proposed as a starting material should be separated from the final intermediate by several one or more reaction steps. that result in isolated and purified intermediates.	"Several" is very unclear and not science based. The number of steps to be filed should be based on the science and not on a preconceived number of steps. Recommend deleting the expectation of isolation and purification of intermediates because many reaction steps are selective enough without isolation or purification of the intermediate to remove any potential carryover of impurities.	1

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1744	Att 1 - Starting Material		Having several one or more reaction steps and associated purification and isolation steps , separating the starting material and the final intermediate reduces the risk that changes in the manufacturing steps prior to the starting material would adversely affect the identity, quality, purity, or potency of the drug substance as these factors relate to the safety and efficacy of the drug product.	"Several" is very unclear and not science based. The number of steps to be filed should based on the science and not on a preconceived number of steps. Recommend deleting the expectation of isolation and purification of intermediates because many reaction steps are selective enough without isolation or purification of the intermediate to remove any potential carryover of impurities .	1
1754	Att 1 - Starting Material		The reaction step that produces the final intermediate can be counted as a reaction step for purposes of evaluating propinquity if the final intermediate is isolated and purified .	Implies that additional purification is needed after isolation. The specification should be adequate, there should not be a "global requirement" for purification of the final intermediate. Appropriate testing of isolated intermediates is already discussed in line 816.	1
1756	Att 1 - Starting Material		An interconversion of a salt to or from its free acid or base form at an intermediate may should not be counted as a reaction step for the purpose of evaluating propinquity provided that interconversion has a purifying effect.	Salt formation should not be counted as a step after the final intermediate but may be counted as a reaction step prior to the final intermediate if it has purifying effect.	1
1759	Att 1 - Starting Material		Isolated and purified intermediates are typically obtained by filtration or centrifugation, fractional distillation from a mixture, or chromatographic procedures. A key element in each of these examples is that some removal of organic impurities usually results from the isolation operation. An operation should not be considered to produce an isolated and purified intermediate if some purification of this nature does not simultaneously take place. For example, evaporating solvent from a reaction mixture or the extraction work up of a reaction mixture is not considered to produce an isolated and purified intermediate.	Propinquity should address number of steps. Purification of impurities should be discussed under C. Carryover of Impurities	1
1768	Att 1 - Starting Material		B. Isolated and purified	Quality of the starting material has to be controlled by appropriate acceptance criteria instead of using the mark 'purified'.	1
1770	Att 1 - Starting Material		A chemical proposed as a starting material should be an isolated and purified substance with defined specifications capable of ensuring the identity, quality, purity or potency of the drug substance.	Quality of the starting material has to be controlled by appropriate acceptance criteria instead of using the description 'purified'.	1

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1771	Att 1 - Starting Material		Identification of an isolated and purified substance as the starting material, as opposed to an in situ and/or crude substance reduces the risk of degradants and/or impurities affecting the identity, quality, purity, or potency of the drug substance.	Quality of the starting material has to be controlled by appropriate acceptance criteria instead of using the description 'purified'.	1
1776	Att 1 - Starting Material		If a chemical proposed as a starting material is the source of significant levels of impurities in the drug substance this should be explained taking into account the qualified level of each impurity that is individually listed in the drug substance specification.	Recommend adding this sentence to the beginning of this section to acknowledge that the Starting Material may contribute impurities that affect the impurity profile of the API provided that these Starting Material impurities are controlled to ensure the API impurities meet the qualified levels..	1
1777	Att 1 - Starting Material		A chemical proposed as a starting material should not be the source of significant levels of unqualified impurities in the drug substance. Reference Q3AR.	The addition of the word "unqualified" in this sentence together with the proposed additional sentence should clarify the difference in impact on qualified and unqualified impurities. Also added reference to ICH for clarity.	1
1784	Att 1 - Starting Material		For purposes of selecting proposed starting materials, a significant level is considered to be greater than 0.10 0.15 percent in the drug substance (0.20 percent for veterinary drug substances not used in human drug products) of any of the following impurities:	Recommend tying the concept of significant level of impurity to the ICH Q3A qualification level. Change to 0.10 to 0.15 to be consistent with Q3A for qualification level and 0.2 to be consistent with VICH GL10	1
1803	Att 1 - Starting Material		There is increased risk to the identity, quality, purity, or potency of the drug substance if a chemical cannot be readily distinguished from its potential isomers and analogs. Moreover, a chemical with a complex molecular structure (e.g., multiple chiral centers) are usually produced through complex synthetic pathways, which can also increase the risk. A proposed starting material typically should possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism for it to be considered readily distinguishable.	This is not a scientific basis for determining starting material. Limiting the number of stereogenic centers in the starting material is not appropriate. What is appropriate is a specification that will adequately control the quality of the starting material regardless of the number of functional groups.	1

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1811	Att 1 - Starting Material		However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex.	Delete examples. These are restrictive and will make the document obsolete as analytical methodology improves	1
1815	Att 1 - Starting Material		If advanced techniques suitable for complex structures (1H-NMR, 13C NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not normally an appropriate candidate for designation as a starting material.	Delete examples. This are restrictive and will make the document obsolete as analytical methodology improves.	1
1831-1841	Att 1 - Starting Material		Flow diagram of the complete synthesis (whole section B)	The criteria set forth in the Guidance should be adequate for defining the starting material. The route of synthesis should be irrelevant. Delete the whole section B about 'flow diagram of the complete synthesis'. This information could be discussed with FDA to support the chosen starting material but should not be included in the filing.	1
1845	Att 1 - Starting Material		A specification for each proposed starting material should be provided and the rationale for the specification explained . Each specification should be based on the quality of the material used to prepare the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E of this guidance).	Specifications are typically based on all batches that have been made, not just the batches that were used for establishing the spec of the drug substance.	1
1859	Att 1 - Starting Material		Moreover, for late stage starting materials FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that an appropriate limit should of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products)	It should be clear that is more important for late stage starting materials than for syntheses where the starting material is more synthetic steps away from the API. The robustness of the process should be used to determine the limit for unspecified impurities. It should not be globally set at 0.10%.	1

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1886	Att 1 - Starting Material		Confirmation that (1) the drug substance manufacturer did not synthesize the chemical, or arrange for another firm to synthesize it, to produce drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (2) an existing manufacturer of the chemical did not scale up its process to produce sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); and (3) the method of manufacture was not provided by the drug substance manufacturer to the other firms that manufacture the chemical (i.e., no technology transfer occurred).	Redundant with the definition of starting material with a significant non-pharmaceutical market. Often a material may initially be manufactured by the drug substance manufacturer, then the material later becomes commercially available.	1
1901	Att 1 - Starting Material		Data (e.g., carryover of impurities) used to justify the proposed starting material should be from batches manufactured by the proposed drug substance manufacturing process. If data from batches produced by other manufacturing processes are also used, the data should be clearly identified as supporting data and or the differences in these manufacturing processes and the proposed manufacturing process should be described	Clarify that this applies to the drug substance manufacturing process not the process to manufacture the starting material. Data from different processes (e.g. laboratory studies to determine fate of impurities) may be appropriate provided differences are explained and justified. All the data is supporting data.	1
1909	Att 1 - Starting Material		The flow diagram provided in S.2.23 will indicate the separation between the final intermediate and the proposed starting material. A cross-reference to the flow diagram in S.2.23 is sufficient.	The flow diagram in S.2.2 which shows the process from the starting material to the drug substance is adequate to show the propinquity.	1
1913	Att 1 - Starting Material		b. Isolated and Purified Substances	Quality of the starting material has to be controlled by appropriate acceptance criteria instead of using the description 'purified'.	1
1915	Att 1 - Starting Material		The starting material specification and the flow diagrams provided in S.2.23 should indicate whether a proposed starting material is an isolated and purified substance.	The flow diagram in S.2.2 which shows the process from the starting material to the drug substance is adequate to show the propinquity.	1

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1921-1957	Att 1 - Starting Material		<p>Delete text 1921-1957 and replace with: The applicant should provide a clear science-based explanation of how the quality of the starting material is related to the impurity profile of the finished drug substance.</p> <p>The scientific rationale and data to support this explanation may take different forms depending on the specific starting material, the process and the finished drug substance. The justification and supporting data should demonstrate that the quality of the proposed starting material as controlled by the starting material specification is appropriate to ensure the consistent chemical quality of the finished drug substance in accordance with its specification.</p>	This section should allow flexibility in the approaches taken to justify the the carryover of impurities and to demonstrate that the quality of the proposed starting material (as controlled by the starting material specification) is appropriate to ensure the consistent chemical quality of the finished drug substance (in accordance with its specification).	1
1964	Att 1 - Starting Material		<p>However, if the chemical structure of the proposed starting material is sufficiently complex, information should be provided to support that the starting material is readily distinguishable from potential isomers and analogs using common instrumental techniques (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy).</p>	Delete examples. These are restrictive and will make the document obsolete as analytical methodology improves.	1
1968	Att 1 - Starting Material		<p>Applicants should provide data (e.g., analytical, spectra) comparing the proposed starting material to a reasonable selection of isomers and analogs to demonstrate that the identification tests specification methods for the proposed starting material are sufficiently specific</p>	Should take into account all tests not just the identification tests.	1
1976	Att 1 - Starting Material		<p>When a starting material has been designated in and approved as part of an application, postapproval changes to the manufacturing process of the approved starting materials, including changes in the route of its synthesis, need not be reported to the Agency unless a commitment to report such changes was included in the approved application.</p>	A Starting Material should be approved based on its specification and impact on downstream process. No upstream process or synthetic route should need to be filed. Therefore this paragraph should not be needed.	1
1995	Att 2 - Starting Material		<p>or body fluid and/or the well characterized extracts from which the drug substance is derived to be starting material for a drug substance derived from a biological source</p>	The first point at which the starting material is appropriate for characterization.	1

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1996	Att 2 - Starting Material		Identification of the biological source and/or the well characterized extracts from which the drug substance is derived to be starting material for a drug substance derived from a biological source	The first point at which the starting material is appropriate for characterization.	1
1998	Att 2 - Starting Material		The term drug substance derived from a biological source includes drug substances that are the chemical obtained directly from the biological source and semisynthetic drug substances that are produced by modification of a chemical (i.e., intermediate) obtained from the biological source	Move to Glossary.	1
2031	Att 2 - Starting Material		The following should be provided for plant starting materials if applicable :	It is not applicable for all requested items if "well characterized extract" is inserted at line 1995.	1
2038	Att 2 - Starting Material		Where possible , a list of pesticides	It may not always be available if starting with "well characterized extracts".	1
2061	Att 2 - Starting Material		For semisynthetic drug substances, the flow diagram should depict the manufacturing process that results in the chemical (i.e., intermediate) from the biological source and/or the well characterized extracts and the synthetic part of the manufacturing process	The first point at which the starting material is appropriate for characterization.	1
2072	Att 2 - Starting Material		taxonomic authenticity	This needs to be defined in Glossary.	1
2099	Att 2 - Starting Material		Changes that have an impact on the final API in the information on plant or animal starting materials (see section I.A of this attachment) should be reported to the Agency in a prior approval supplement.	"Changes in information" is too vague and over restrictive. This should align with guidance documents on post approval changes.	1
2151	Glossary		In-process Material Tests: Measures used to assess the quality attributes of an intermediate, postsynthesis material, or unfinished drug substance and/or their suitability for use in the manufacturing process	The word "in-process" should be deleted so that "material test" refers to any test on intermediates, post synthesis materials, unfinished drug substance, etc. Also provides consistency in that material tests are done on isolated materials not in-line or at-line testing.	1
2168	Glossary		Intermediate Tests: Measures used to assess the quality attributes of an intermediate and/or its suitability for use in the manufacturing process	Covered under "Material Test".	1

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2192	Glossary		Postsynthesis Material Tests: Measures used to assess the quality attributes of a postsynthesis material and/or its suitability for use in the manufacturing process	Covered under "Material Test".	1
2195	Glossary		In-Process Controls: Checks performed An all-inclusive term used to describe the controls used during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the an intermediate with an established specification or the drug substance will conform to its respective specification. The term includes operating parameters, environmental controls, process tests, intermediate tests, postsynthesis materials tests, and unfinished drug substance tests.	Consistency with ICH Q7A.	1
2195	Glossary		Process Controls: see In-Process Controls	Covered under In-Process Controls.	1
2200	Glossary		Process Tests: Measures used to monitor and assess the performance of the process (e.g., a test to evaluate reaction progress)	Covered under In-Process Controls.	1
2203	Glossary		Reaction Step: A unit operation or number of unit operations that effect a change in the molecular structure of a starting material or intermediate or another type of transformation (e.g. salt formation) that has a demonstrated purifying effect. More than one reaction step can take place sequentially in a single -reaction vessel.	Salt formation should not be counted as a step after the final intermediate but may be counted as a reaction step prior to the final intermediate if it has purifying effect.	1
2205	Glossary		Reagent: A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a drug substance and that has an impact on the conditions of the chemical reaction or contributes a minor structural element to a subsequent product in the synthesis.	Add definition for clarity.	1
2226	Glossary		Solvent: An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of a drug substance	Add definition for clarity.	1

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2248	Glossary		Unfinished Drug Substance Tests: Measures used to assess the quality attributes of an unfinished drug substance and/or its suitability for use in the manufacturing process	Covered under "Material Test".	1